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EXAMINER	
HAGHIGHATIAN, MINA	

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NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/596,817	CASTILE ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/12/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-5, 7, 12, 13, 15, 16 and 32- 37* is/are pending in the application.

4a) Of the above claim(s) *32-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,7,12,13,15,16 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Receipt is acknowledged of the Amendments, Remarks and IDS filed on 10/12/10. Claims 1, 3, 8-11, 14 and 17-19 have been cancelled while claims 4, 7, 12, 13, 15, 16, 32-34 and 36 have been amended. New claim 37 has been added. Accordingly, claims 4-5, 7, 12, 13, 15, 16, 32-37 are pending. Claims 32-36 remain withdrawn. Claims **4-5, 7, 12, 13, 15, 16 and 37** are under examination on the merits.

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application

Restriction

Applicant's election with traverse of Group I, including claims 4-5, 7, 12, 13, 15, 16 and 37 in the reply filed on 10/12/10 is acknowledged. The traversal is on the ground(s) that "Kramer does not teach or suggest the composition or any of the other aspects of the invention claimed in Groups I to V. Therefore, all of the invention Groups have the same or a corresponding special technical feature". This is not persuasive because at the time of restriction (before cancellation of claim 1) Kramer anticipated each and every element of the claims of Group I and as such was a properly employed as a reference showing special technical feature. Applicant also argues that "all of

process claims of Groups Ii to IV and the device of Group V depend directly of indirectly from independent claim 37. Therefore, the components of composition claim are incorporated by reference into other dependent claims. A reasonably thorough search and examination of the composition would lead to disclosures of processes for using the composition". This is not persuasive because the fact that all process claims are dependent on the composition claims does not obviate restriction requirement. For example claims drawn to a method of treating a neurological disorder or Parkinson's disorder is not taught by Kramer, Who teaches nasally administered formulations of zolpidem for inducing sleep or treating anxiety. It has been shown that the compositions are different and unrelated to the methods of treatment in claims 32-36.

As Applicants have elected the composition (product) claims, if the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-5, 7, 12, 13, 15 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer et al (US 20040241100) in view of Auh et al (EP 1250925) as evidenced by Loftsson et al (6,699,849).

Kramer et al teach a pharmaceutical composition for nasal administration, which includes **zolpidem**, a pharmaceutically acceptable salt thereof, or a combination

thereof, and a pharmaceutically acceptable nasal carrier in liquid form. Another embodiment of the present invention provides a method for inducing sleep, which includes nasally administering to a subject in need thereof a pharmaceutical composition, which includes zolpidem, a pharmaceutically acceptable salt thereof, or a combination thereof, and a pharmaceutically acceptable nasal carrier in liquid form (see abstract).

Kramer et al disclose advantages of nasal administration of a formulation comprising zolpidem in liquid form. Such advantages include efficient and ease of use, reduced need for supervision of administration, minimized or bypassed first pass metabolism and a beneficial pharmacokinetic profile (see [0014] to [0017]).

The suitable dosage is stated as from 0.001 to 250 mg zolpidem in a carrier in an amount of from 0.002 to 4 ml. This provides a teaching of from 0.5 to 62.5 mg/ml concentration (see [0023]-[0026]).

The compositions may be in a solution form and the carrier may be one or more of water, saline solution, ethanol, polyethylene glycol, propylene glycol etc (see [0035]). Other components that may be added include mucoadhesives such as **chitosan** and penetration enhancers (see 0036]). Suitable salt for the active agent include tartaric acid and tartrate (see [0040] and [0041]). The formulations also comprise a buffer such that the composition has a **pH** of from 3 to 10, or any value in between (see [0038]).

Kramer et al teaches addition of agents such as penetration enhancers but lacks specific disclosure on addition of cyclodextrins. This deficiency is cured by Auh et al.

Auh et al teach nasal spray formulations comprising ondansetron hydrochloride as the active agent and other components such as solubilizer including sulfobutyl ether β–cyclodextrin sodium salt (see abstract). It is disclosed that the solubilizers used such as SBCD, DMCD, 2HPβCD are present in an amount between 7 and 20% by weight based on the weight of the formulation (see [0019]). Auh et al also disclose that if necessary, the said formulations may contain not more than 2% of a water soluble **chitosan** to increase the adhesiveness of the compositions to the nasal mucosa. The pH of the formulations is preferably adjusted to a week acidity of 4 to 6 (see [0021]).

Loftsson et al teach that cyclodextrines act as penetration enhancers by increasing drug availability at the surface of the biological barrier (see col. 4, lines 6-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have implemented the teachings of Auh et al in the formulations of Kramer et al because Kramer et al teach nasal formulations comprising zolpidem, chitosan and penetration enhancers. Auh et al disclose that cyclodextrins are suitable solubilizers for nasal formulations and as it is evident from Loftsson et al, cyclodextrins also act as penetration enhancers. Furthermore, Auh et al teaches that addition of chitosan to the said formulations increases the adhesiveness of the formulations to the nasal mucosa. Thus, it would have been obvious to one of ordinary skill in the art to have chosen cyclodextrins for the nasal formulations of Kramer because one would have known from the art that cyclodextrins are both suitable solubilizers and penetration

enhancers for nasal formulations. In other words, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Furthermore, the claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer et al (US 20040241100) in view of Auh et al (EP 1250925) as applied to claim 37 above, and in further view of Birch et al (WO 03080021).

Kramer and Auh et al have been discussed above. Their combination lacks disclosure on the chitosan salt being chitosan glutamate or its amount. These deficiencies are cured by Birch et al.

Birch et al teach aqueous formulations suitable for intranasal administration comprising buprenorphine and a pectin or chitosan. Such formulations can induce rapid and prolonged analgesia when delivered intranasally to a patient (see abstract). An aqueous solution formulation for intranasal administration comprises a) from 0.1 to 10

mg/ml of buprenorphine, b) from 0.1 to 20 mg/ml of a **chitosan** and c) from 0.1 to 15 mg/ml of HPMC. The solution has a pH of from 3 to 4.8 (see page 3, embodiment 2).

Birch et al also disclose that preferred salts of **chitosan are glutamate** and chloride (see page 12, lines 1-5 and 21-24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the general teachings of nasal formulations comprising an active agent such as zolpidem, cyclodextrin derivative and a chitosan as taught by Kramer and Auh et al, to have looked in the art for the specific and suitable salts of chitosan and amounts of it for nasal formulations as disclosed by Birch et al with the reasonable expectation of preparing efficient, stable and suitable formulations for nasal administration. In other words, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Furthermore, the claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

Claims 4-5, 7, 12, 13, 15, 16 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (WO 03095498, in Japanese provided by

Applicants and as evidenced by its US equivalent document US 20050215520) in view of Birch et al (WO 03080021) as evidenced by Illum (Nasal drug delivery: new developments and strategies, provided by Applicants in the IDS of 03/01/07).

Liu et al teach a sterile water-soluble complex of water-insoluble or sparingly-soluble organic medicines and beta-cyclodextrin derivatives. A fully-water-soluble complex can be prepared from any water-insoluble or sparingly-soluble organic medicines or other organic compounds (see abstract). One suitable active agent for the said drug-cyclodextrin complex formulation is **zolpidem** (see Table 1). Example 2 also discloses a formulation comprising zolpidem and a cyclodextrin derivative.

Liu et al lacks specific disclosure on the addition and the amount of chitosan. However these deficiencies are cured by Birch et al.

Birch et al teach aqueous formulations suitable for intranasal administration comprising buprenorphine and a pectin or chitosan. Such formulations can induce rapid and prolonged analgesia when delivered intranasally to a patient (see abstract). An aqueous solution formulation for intranasal administration comprises a) from 0.1 to 10 mg/ml of buprenorphine, b) from 0.1 to 20 mg/ml of a **chitosan** and c) from 0.1 to 15 mg/ml of HPMC. The solution has a pH of from 3 to 4.8 (see page 3, embodiment 2).

Birch et al also disclose that preferred salts of chitosan are glutamate and chloride (see page 12, lines 1-5 and 21-24). The formulations may also comprise an

absorption promoting agent including chitosans, surface active agents, cyclodextrins, etc (see page 19, lines 16-20).

Illum teach strategies found on nasal delivery of active agents. It is disclosed that to improve absorption of active agents from nasal mucosa, compounds can be added such as **cyclodextrins** and **chitosan glutamate**. Illum teach that "it is possible to greatly improve the nasal absorption of polar drugs by administering them in combination with an absorption enhancer that promotes the transport of the drug across the nasal membrane". It is also disclosed that an example of such absorption enhancer is dimethyl-β-cyclodextrin (see page 1186, 2nd column). Illum also discloses that chitosan is known as a nasal delivery system that is able to efficiently deliver polar drugs to the systemic circulation. Chitosan glutamate is recited as an acceptable salt (see page 1187, 1st column). In Figure 4, it is shown that intranasal solution of morphine and chitosan has the same Cmax as intravenous morphine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the nasal formulations of Liu et al comprising active agents such as zolpidem complexed with cyclodextrins with the teachings of Birch et al on the advantages of adding chitosans such as chitosan glutamate in the nasal formulations for its benefits to the formulations. One of ordinary skill in the art would have been motivated to have combined zolpidem-cyclodextrin and chitosan glutamate because the advantages of both cyclodextrins and chitosans in nasal

formulations are disclosed and one would have been motivated to improve the absorption and with the reasonable expectation of success in broadening the scope of the disclosed nasal formulations to other active agents for treating other disorders with the same rapid absorption, efficient and easy to administer delivery systems. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The motivation for substituting them flows from their having been used in the prior art, and from their being recognized in the prior art as useful for the similar purpose. As shown by the recited teachings, instant claims are no more than the substitution of conventional components of active agents. It therefore follows that the instant claims define prima facie obvious subject matter. Cf. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

Claims 4-5, 7, 12, 13, 15, 16 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loftsson et al (US 6,699,849) in view of Kramer et al (US 20040241100) and Illum.

Loftsson et al teach methods for enhancing the complexation efficiency of a drug with cyclodextrin and for enhancing the availability of a drug following administration of a cyclodextrin-drug complex (see abstract). It is disclosed that in aqueous solutions, cyclodextrins form complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug molecule

or more frequently by some lipophilic portion of the drug structure (see col. 2, lines 1-6). It is further disclosed that cyclodextrins act as penetration enhancers by increasing drug availability at the surface of the biological barrier (see col. 4, lines 6-8).

Loftsson et al teach that particularly preferred cyclodextrins for use in the said methods and formulations include **β–cyclodextrin sulfobutyl ether** and hydroxypropyl-β-cyclodextrin, etc (col. 7, lines 4-5 and 56-60). Various active agents such as benzodiazepines have been listed as suitable for the said drug-cyclodextrin complexes (see columns 9 to 11). The said formulations are suitable as nasal sprays and the pH is maintained at levels of below 5 (see col. 10, lines 12-40) and col. 11, lines 42-55). In Example 8, the bioavailability of midazolam and sulfobutylether β-cyclodextrin is shown.

Loftsson et al lack specific disclosure on the addition of chitosan and the active agent being zolpidem. These deficiencies are cured by Kramer et al and Illum.

Kramer et al, discussed above teach nasal formulations comprising zolpidem or a salt thereof such as tartrate and chitosan.

Illum teach strategies found on nasal delivery of active agents. It is disclosed that to improve absorption of active agents from nasal mucosa, compounds can be added such as cyclodextrins and **chitosan glutamate**. Illum teach that “it is possible to greatly improve the nasal absorption of polar drugs by administering them in combination with an absorption enhancer that promotes the transport of the drug across the nasal membrane”. It is also disclosed that an example of such absorption enhancer is

dimethyl-β-cyclodextrin (see page 1186, 2nd column). Illum also discloses that chitosan is known as a nasal delivery system that is able to efficiently deliver polar drugs to the systemic circulation. Chitosan glutamate is recited as an acceptable salt (see page 1187, 1st column). In Figure 4, it is shown that intranasal solution of morphine and chitosan has the same Cmax as intravenous morphine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the general teachings of Loftsson et al on nasal formulations to have looked in the art for other active agents and other additives such as chitosan suitable for the said nasal formulations, as taught by Kramer et al and Illum, with the reasonable expectation of success in broadening the scope of the disclosed nasal formulations to other active agents for treating other disorders with the same rapid absorption, efficient and easy to administer delivery systems. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The motivation for substituting them flows from their having been used in the prior art, and from their being recognized in the prior art as useful for the similar purpose. As shown by the recited teachings, instant claims are no more than the substitution of conventional components of active agents. It therefore follows that the instant claims define prima facie obvious subject matter. Cf. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

Also while Kramer et al does not teach the specific salt of chitosan, Illum clearly teaches that chitosan glutamet is a preferred salt of chitosan for nasal formulations. It would have been obvious to one of ordinary skill in the art to have selected chitosan glutamate as taught by Illum for the nasal formulations of the combined references.

Response to Declaration of Dr. Castile

Dr. Castile's Declaration filed on 10/12/10 has been fully considered, but is not sufficient to overcome the rejection. The Declaration mainly argues that it would not have been obvious to one of ordinary skill in the art to have combined the Auh et al reference with Kramer et al reference because the experiments show the unpredictable nature of use of cyclodextrins and chitosan in combination with various drugs. Declaration relies on experiments performed based on the Auh et al reference and the instant specification and concludes that ondansetron with both cyclodextrin and chitosan had lower bioavailability than ondansetron with cyclodextrin alone.

This is not persuasive because the rejection was based on the teachings of Kramer et al in view of Auh et al. That is the Kramer et al reference teaches nasal formulations comprising chitosan and a penetration enhancer. Auh et al was relied upon for its teachings of cyclodextrins such as sulfobutyl ether-β-cyclodextrin being excellent solubilizers. However, it is well documented that cyclodetxrins also act as a penetration enhancer (see Loftsson et al, col. 4 and Illum, page 1186) for the nasal formulations. Accordingly, it has been shown that there is sufficient motivation for one of ordinary skill

in the art, looking at the disclosure of Kramer et al, to have looked in the art for a teaching on suitable penetration enhancers for nasal formulations.

For a Declaration to persuasively show unexpectedness based on the combination of prior art references, the comparison has to be side-by-side and between the closest prior art and the invention. Here Auh et al was supportive reference and relied upon for its teachings on the advantages of adding cyclodextrins.

Response to Arguments

Applicant's arguments with respect to claims 1, 3-5, 7-19 have been considered but are moot in view of the new ground(s) of rejection. However as some prior art documents are employed in the new rejection, relevant arguments will be responded to.

Applicant argues that Kramer does not disclose a chitosan, a salt, or a derivative thereof or a salt of a derivative thereof, but merely incidentally discloses among many other ingredients, a chitosan hydroxycellulose in paragraph [0036], a compound which is believed not to exist. Even if such a compound does exist and even if chitosan and hyroxycellulose were intended to be presented as separate components, the Kramer disclosure is not an enabling disclosure. Moreover, even if a skilled person decided to follow the teaching of paragraph [0036] of Kramer and use a mucoadhesive in the composition of Kramer, the skilled person would have had a choice of no less than five listed mucoadhesives (which are merely examples of mucoadhesives that could be used). However, in the absence of any examples or more specific embodiments in

Kramer, there is nothing to motivate the skilled person to select any one of the many possible ingredients in preference to any other ingredient.

Applicants arguments are not persuasive because Kramer et al is clearly teaching nasal formulations comprising zolpidem and that other **preferable** compounds that may be included in the composition include mucoadhesives such as chitosan and penetration enhancers (see [0036]). The suggested mucoadhesives contains a short list of five compounds. This is a finite list and no undue experimentation would be required on the part of one of ordinary skill in the rat to test even all five compounds and choose the best choice for the desired active agent. It has been held that a reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

Furthermore, as applicants are not required to, the prior art is also not required to exemplify every working embodiment. It is well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the submitted knowledge in the art, to a person of ordinary skill in the art. In re Boe, 355, F.2d 961, 148 USPQ 510, 510 (CCPA 1966).

There is clearly a teaching by Kramer et al that chitosan and a penetration enhancer are preferably added to the nasal formulations comprising zolpidem. Auh et al on the other hand, not only teaches that cyclodextrins such as sulfobutyl ether-β-cyclodextrin are excellent solibulizers for insoluble or hardly soluble active agents, it

also teaches that chitosan, a mucoadhesive, may be added to the nasal formulations to increase the adhesiveness of the composition to the nasal mucosa. Additionally, Loftsson has been employed to show that cyclodextrins act as penetration enhancers in nasal formulations.

Applicant's arguments that "There are very distinct advantages, unrecognized by those skilled in the art prior to the present invention, including Kramer and Auh et al, associated with using chitosan in combination with SBE-CD in an aqueous composition for the nasal delivery of zolpidem. As explained at page 3, fourth paragraph, of the present application as filed, relatively high concentrations of zolpidem are required in order to effectively treat insomnia using a composition delivered via the intranasal route. The concentrations required are above the reported aqueous solubility of zolpidem tartrate as published in the Merck Index (Dr. Castile Declaration, paragraph 16 and Exhibit B). It has been found that the inclusion of SBE-CD in the compositions of the invention enhances the aqueous solubility of zolpidem (and its salts). This means that compositions comprising zolpidem in a concentration suitable for nasal delivery for the treatment of insomnia can be provided" is also not persuasive. 1) Kramer et al teach nasal formulations comprising a dosage of up to 62.5 mg/ml of zolpidem, which is well within the claimed concentration range. 2) It has been shown and it is well documented that cyclodextrins are excellent solubilizers, especially for insoluble drugs. Thus it is not considered inventive to claim that a higher amount of zolpidem can be dissolved in a formulation comprising cyclodextrin. 3) Loftsson et al clearly teach that "In solution, the

complexes are usually prepared by addition of **an excess amount** of the drug to an aqueous cyclodextrin solution (see col. 2, lines 26-28).

Applicant further states that "Additionally, the inclusion of chitosan in the compositions of the invention increases the bioavailability of the zolpidem. See Example 5 of the present application. The combination of increased drug solubility and improved bioavailability provides an aqueous composition that can be very effective for the treatment of conditions such as insomnia. The compositions described in Auh comprise a complex base material consisting of (i) 70 to 85% by weight of water, (ii) 5 to 15% by weight of polyethylene glycol, (iii) 0.005-0.02% by weight benzalkonium chloride and (iv) 7 to 20% by weight of one stabilizer selected from SBE- CD sodium salt, dimethyl-l)-cyclodextrin and 2-hydroxypropyl-13-cyclodextrin. It is clear from the disclosure of Auh that this disclosed combination of the ingredients of the base material is required in order to give the compositions described in Auh the required properties. See, for example, paragraph [0016] of Auh. The skilled person reading Auh would not have contemplated moving away from Auh's essential teaching and selecting just one of the essential ingredients of the base material to use in these compositions.". This is neither persuasive nor commensurate in scope with the claims. 1) In view of the references of record, it is not surprising or unexpected to state that "The combination of increased drug solubility and improved bioavailability provides an aqueous composition that can be very effective for the treatment of conditions such as insomnia. It has been shown by the references cited that one would expect a formulation comprising cyclodextrin and chitosan to have increased drug solubility and bioavailability. Cyclodextrins are

disclosed as solubilizers and chitosan is disclosed as a mucoadhesive improving drug permeation. Furthermore, cyclodextrin is also a known penetration enhancer. 2) Auh et al discloses formulations comprising active agent (ondansetron), water, benzalkonium chloride, polyetheylen glycol and cyclodextrin, all of which are employed by the instant invention. Furthermore, the claims employ the open-ended transition phrase of “comprising" which allows for other non-recited components being present. As such Applicants arguments that “one of skill would not have contemplated moving away from Auh’s essential teachings…” is not commensurate with the scope of claims.

It is then argued that “Loftsson describes a method for enhancing the complexation efficiency of a benzodiazepine with a cyclodextrin. The conditions used in Loftsson are designed to "ring open" a proportion of the benzodiazepine molecules in order to optimize complexation. There is no mention of zolpidem or of compounds with a similar structure to zolpidem. There is nothing in Loftsson to suggest that zolpidem could undergo "ring opening" under the condition used in Loftsson, or even that this would be desirable. The disclosure of Loftsson seems completely irrelevant to the present application”. This is not persuasive because while Loftsson et al’s preferred embodiments are to formulations comprising a complex of cyclodextrin and an active agent such as benzodiazepines, they clearly teach that cyclodextrins are suitable solubilizers for many active agents. For example, in column 2, it is disclosed “In aqueous solutions, cyclodextrins form complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug or more frequently, by some lipophilic portion of the drug structure (see lines 2-6).

In the paragraph bridging columns 3 and 4, Loftsson et al recite "It is **generally** recognized that cyclodextrins act as true carriers by keeping the hydrophobic drug molecules in solution and deliver them to the surfaces of the biological membrane, e.g. skin, mucosa….". In fact the entire section of "Background of the Invention" which describes advantages of adding cyclodextrins to drugs to form complexes, does not disclose benzodiazepines.

It then, would have been obvious to one of ordinary skill in the art to have looked in the art for other suitable active agents that can be formulated for nasal delivery and benefit form complexing with cyclodextrins.

In response to applicant's argument that the references do not disclose any particular embodiment, or that they should not be combined, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In summary, it has been shown that there exists an overwhelming disclosure in the prior art on the advantages of adding cyclodextrins such as SBE-CD and chitosan glutamate to insoluble or hardly soluble drugs such as zolpidem. As such one of ordinary skill in the art would be highly motivated to make the formulations according to the said teachings, with reasonable expectation of preparing an effective formulation for nasal administration.

Conclusion

Claims **4-5, 7, 12, 13, 15, 16 and 37** are rejected. Claims **32-36** remain withdrawn**.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616